Interpreting QFT results in US HCWs: A Statistical Analysis

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The Plan
* No conflicts of interest *

The problem with reversions and publications
The probability based on prevalence
Problem-solving: Why use an ROC?
Published results
Pre-publication expanded dataset
PPP/PPN
Interpretation and Conclusion

The Problem with Reversions

"But doctor, I've never been sick a day in my life!"

Approach is clinically driven
What do you do with an unexpected positive result?

TST vs. IGRA testing
n = 5,702 HCWs

Pre-IGRA (TST positives)

The Papers

Infection Control and Hospital Epidemiology, April 2013
A summary of meeting proceedings on 'Addressing Variability Around the Cut-point in Serial Interferon Gamma Release Assay Testing'

PLoS One, January 2013
Repeat IGRA Testing in Canadian Health Workers: Conversions or Unexplained Variability?
A Zwerling, A Benedetti … D Menzies, M Pai

Journal of Occupational Medicine and Toxicology, 2012
Interferon-gamma release assays for the tuberculosis serial testing of healthcare workers: a systematic review
Felix Ringshausen, Anja Schablon, Albert Nienhaus

Am J Respir Crit Care Med, January 2013
Test Variability of the QuantiFERON-TB Gold In-Tube Assay in Clinical Practice
J Metcalfe, A Cattamanchi… E. Graviss

CHEST, July 2012
To Repeat or Not to Repeat--That Is the Question!
R Loddenkemper, R Diel, A Nienhaus

The Papers on Variability

JCM, September 2012
Investigation of False-Positive Results Given by the QuantiFERON-TB Gold In-Tube Assay
Madeline Slater, Julie Parsonnet, Niaz Banaei

Unusual Interferon Gamma Measurements with QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube Tests
R Powell, W Whitworth, J Bernardo, P Moonan, G Mazurek

Within Subject Variability of Interferon-g Assay Results for Tuberculosis and Boosting Effect of Tuberculin Skin Testing: A Systematic Review
Richard N. van Zyl-Smit, Alice Zwerling, Keertan Dheda, Madhukar Pai

J Clin Microbiol. August 2010
Immediate Incubation Reduces Indeterminate Results for QuantiFERON-TB Gold In-Tube Assay
Victor Herrera, Ellen Yeh, Kelly Murphy, Julie Parsonnet, Niaz Banaei

Within-Subject Interlaboratory Variability of QuantiFERON-TB Gold In-Tube Tests
W Whitworth, L Hamilton, D Goodwin, C Barrera, K West, L Racster, L Daniels, S Chuke, B Campbell, J Bohanon, A Jaffar, W Drane, D Maserang, G Mazurek
... and what they say

- Pai M and O'Brian R, Pmed 2007
  "...need to establish new definitions for conversion or reversion other than dichotomous way defined by CDC"
- Fong et al, CHEST 2012
  "Criteria for defining conversions and reversion by establishing new cut-offs needs further evaluation..."
- Loddenkemper, Diet, Nienhaus, CHEST 2013
  "It is quite arbitrary to limit true conversion to those with a second QFT-GIT of >1.0 IU/mL, since that value... has not been validated. Other authors have proposed a threshold of 0.5 or 0.7 IU/mL or a minimum increase of the interferon-γ concentration."

Probability Based on Prevalence

A small error applied over a large population produces a non-negligible number of subjects who are incorrectly classified as having the condition.

Why we Expect Reversions

If a test has 99% sensitivity and specificity, and \( n = 4,000 \)

**Prevalence 50%:**
- 2,000 with disease / 2,000 without disease
- 1% x 2,000 = 20 false negative
- 1% x 2,000 = 20 false positive (PPV 99%)

**Prevalence 5%:**
- 200 with disease / 3,800 without disease
- 1% x 200 with disease = 2 false negative
- 1% x 3,800 without disease = 38 false positive (PPV 84%)

38 false positives of 200 true positives can appear to be ~20% false positive rate, but in fact remains only 1% (38/3838)

TST vs. IGRA testing; \( n = 28,828 \) QFTs

Pre-IGRA (TST positives)
Who has TB?

Early ROC4s

Serially tested positive US HCWs
- \( n = 153 \) from Palo Alto Veterans Hospital
  - age
  - TST status
- Added 612 from University Illinois, Chicago
  And 66 from The Cleveland Clinic, \( n = 852 \)
  - age
  - time between tests

Why use ROC4s?

Receiver Operating Characteristic analysis differentiates similar-appearing groups based on attributes
Published Results

Delineating a Retesting Zone Using Receiver Operating Characteristic Analysis on Serial QuantiFERON Tuberculosis Test Results in US Healthcare Workers
Wendy Fromme, Jon Salt, Dario Hernandez, Jeffrey Nusell, Paul Trepeluk, David Melder and Jessica Young

We used statistical modeling to derive the optimal point for defining a retesting zone.

TBESC Task Order #18
n=2,500 HCWs

- Conversions with IGRA occurred most frequently in those who’s baseline result was close to the cut-point.
  Conversion rates: TSPOT 8.3 %
  QFT 6.1 %
  TST 1.0 %

- Most IGRA conversions do not represent true change in infection status.
  ~75% of IGRA conversions were transient.
  Conversion and reversion occurs with all 3 tests, but rates are significantly higher with IGRA than TSTs.

Addition of CDC’s Task Order 18 Data

N = 1,049 Serically Tested US HCWs with Positive Results
  186 from Palo Alto Veterans Hospital
  613 from University Illinois, Chicago
  63 from The Cleveland Clinic
  77 from Mid-Atlantic Department of Health
  71 from New England National TB Center
  7 from South Central DSHS

+ Age
+ Time between tests

Conclusions

A new definition of Conversion/Reversion is needed.
- It took decades to define conversion with TST
- The dichotomous/binary cut-point is inadequate in the low-risk setting.
- Reversions are expected in this setting.

A validated model identifies best-fit retesting zone at
- <1.1 IU/ml
- <0.7 IU/ml and <2.8 IU/ml are options

The time between tests does not predict reversion.
Age has an influence on QFT reversions with higher values
We can predict reversion after 2 low-positive tests as well

Collaborators and Colleagues

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Thank You